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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/954,571	09/11/2001	Kenneth R. Chien	041673-1001	7236

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 02/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/954,571	CHIEN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-72 and 77-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *70-72 and 77-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 11/14/05 has been acknowledged.

Claims 70-72 and 77-97 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 80-82 and 84-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter). The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the same reasons of record as set forth in the office action mailed on 6/14/05.

The instant claims are drawn to various transdominant negative PLB genes, which are not disclosed on pages 10-11 of instant specification. As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." So claims 80-82 and 84-85 are apparently new matter. No pages or place in the specification support this amendment. A careful review by the examiner of the specification failed to identify any support for this new limitation. Since no basis has been found to support the new claim limitation in the specification, the claims are rejected as incorporating new matter.

Response to arguments (New matter)

The applicant arguments regarding new matter issue on pages 6-7 of response filed on 11/14/05 has been fully considered. The applicant argues that the instant claims has been amended to over come the instant rejection. However, applicant's arguments are found not persuasive because the applicant fails to amend the instant claim and there is no support these claim in example-2 of the specification as filed. Thus the instant rejection has been maintained.

Claims *70-72 and 77-97* are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for delivering a therapeutic dose of a transdominant negative phospholamban (S16E PLB) to enhance SERCA-2 activity in order to treat cardiac contractility and reduce the reoccurrence of interstitial fibrosis by intra-coronary gene administering an AAV encoding transdominant negative phospholamban containing a mutation at amino acid 16 from serine (S) to glutamic acid (E), does not reasonably provide enablement for a method of delivering a therapeutic dose of any other PLB mutant, which is capable of treating any cardiac disease caused by any and all factors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the office action mailed on 6/14/05.

Nature Of Invention:

The instant invention relates to treatment of a heart disease via a method of gene therapy.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope invention as claimed encompasses a method of delivering a therapeutic dose of an expression vector (viral or non-viral) encoding a mutated phospholamban gene (PLB) to the cardiac muscle in order to treat any and all heart diseases. The specification teaches the expression of dominant negative phospholamban disrupts the function of the wild type protein. The specification teaches an adeno-associated vector (AAV-S16EPLB) that encodes a phospholamban transdominant mutant S16EPLB by replacing Ser16 with the basic amino acid glutamine, thereby introducing a negative charge at position 16. At best the specification teaches intra-coronary administration of the

AdenoS16EPLB significantly enhanced cardiac contractility indicated by an approximately 33% increase in mean velocity of circumferential fiber shortening (mVcf) 6 days after transfection (example-7). Besides increasing cardiac contractility by an intra-coronary administration of the AdenoS16EPLB, the specification fails to disclose the treatment of any other cardiac disease caused by factors other than phospholamban and SERCA-2 interaction.

State Of Art And Predictability:

The scope of the instant invention encompasses genetic modification of a cell in-vivo, therefore the invention falls in the realm of gene therapy. The gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy (see Juengst BMJ, 326:1410-11, 2003; Check NATURE 422:7, 2003; Couzin et al, SCIENCE 307:1028, 2005; Rosenberg et al, SCIENCE 287:1751, 2000; Anderson, NATURE 392:25-30, 1998; Touchette, NAT. MED. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectation of current gene therapy protocols have been over sold without any apparent success. The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease.

In instant case the state of the art regarding the "phospholamban hypothesis" in heart failure is complex and highly unpredictable, since phospholamban erasure does not cure hypertrophy or overall ventricular function in the setting of experimental heart failure due to over expression of tropomodulin Gαq or a mutant myosin binding protein C, although the characteristically prolonged cardiomyocyte calcium transients and enhanced unloaded fractional shortening were rescued. Furthermore phospholamban ablation only incompletely healed a mouse model of hypertrophic cardiomyopathy due to expression of a mutant myosin heavy chain, and did not improve the progressive demise of the pressure-overloaded mouse heart resulting from chronic aortic stenosis. Therefore the heart failure is more likely a clinical entity characterized largely by its overwhelming complexity rather than by the instigating cause(s), it starts to seem unlikely that one single approach (e.g., phosholamban antagonism) will ever benefit all cases of human heart failure. A uniform conclusion that does emerge from these efforts is that we still have very limited understanding about the full complexity of one single aspect of heart muscle physiology (calcium handling), let alone the exponential complexity of human heart disease in general (see Armand et al CARDIOVASC RES. 62(3):439-41. 2004, Janczewski et al CARDIOVASC RES. 62(3):468-80, 2004). In instant case the scope of instant invention encompasses the treatment of any heart disease including heart failure, cardiac contractility and relaxation, regulation of calcium handling in cardiomyocytes and regulation of calcium uptake into-sacro-

endoplasmic reticulum in cardiac cells by administering any viral vector encoding any mutant of phospholamban gene. Considering the complexities involved the etiology of a particular heart disease the instant specification fails to provide an enabling disclosure, which establishes a mutant form of phospholamban gene is capable of treating all cardiac diseases. For example considering the instant specification is it is unclear how one skill in the art would treat hypertension or coronary artery disease by administering a mutant phospholamban gene, any fragment thereof or any other gene (as claimed) to the cardiac muscles. The RAC advisory panel clearly emphasized the need for a greater understanding of an underlying mechanism that contributes to a disease along with the pathogenesis of the disease. In addition, besides the use of a phospholamban transdominant negative mutant S16EPLB the specification fails to disclose any other phospholamban mutant, which is capable of enhancing SERCA-2 activity leading enhanced cardiac contractility. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Therefore it would requires an undue amount of experimentation to characterize any other transdominant negative mutant of phospholamban for the claimed biological activities.

Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes. Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in-vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets. In addition there exists an uncertainty about the degree to which a vector's genetic material may integrate into the host genome extends to most types of gene therapy trials. Scientists are also unsure how an insertion could affect a patient, and worry cancer could occasionally be triggered, such as occurred various trials involving gene therapy (see Check Nature 422:7, 2003). Thus the use of any viral vector especially in context with cardiac gene transfer is

considered unpredictable and would require further undue amount of experimentation. Although, the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals. In the instant case the specification as filed discloses intra-coronary administration of adeno-associated vector (AAV-S16EPLB) that leads to gene delivery to heart muscles.

In instant case treating a heart disease via a gene based therapy is not considered routine in the art and without sufficient guidance to a specific heart disorder in context of phosholamban gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. see in re wands 858 f.2d 731, 8 uspq2nd 1400 (fed. cir, 1988). it is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. see ex parte Singh, 17 uspq2d 1714 (bpai 1991). therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Response to arguments (enablement)

The applicant arguments regarding new matter issue on page 8 of response filed on 11/14/05 has been fully considered. The applicant argues that, since claims to gene therapy of cardiac conditions with S16E molecules are enabled by present disclosure, same conclusion should be reached with respect to the amendment and newly added claims. The applicant argues that the hamster model data provided in the spec teaches that PBL inhibition can lead to a chronic reversal of heart failure by employing the AAV mediated gene therapy. However, applicant's arguments are found not persuasive because the scope of invention as claimed encompasses the treatment of any cardiac disease by administering any viral vector encoding PLB-S16E gene, wherein the viral vector is administered to the heard via any route of administration. The earlier office action clearly provided the evidence that such an approach is considered highly unpredictable for cardiac gene therapy. For example the use of retroviral vectors would be highly unpredictable since retroviral vectors require target cells to be in cycling state for the successful delivery of gene of interest. At best the specification as field teaches that intra-coronary administration of an AAV-PBL(S16E) results in increased cardiac

contractility and reduce the reoccurrence of interstitial fibrosis. However considering the scope of invention as claimed, state of the art and the amount of guidance provided in the specification, it is highly unpredictable that one skilled in the art would be able to treat any and all cardiac diseases (i.e. heart failure, cardiac contractility and relaxation, regulation of calcium handling in cardiomyocytes and regulation of calcium uptake into-sacro-endoplasmic reticulum in cardiac cells etc each having considerably distinct etiologies) by mere administration of any viral vector encoding PBL(S16E) to the heart. The earlier office action provides a clear evidence that the state of the art regarding the "phospholamban hypothesis" in heart failure is complex and highly unpredictable (see Armand et al CARDIOVASC RES. 62(3):439-41. 2004, Janczewski et al CARDIOVASC RES. 62(3):468-80, 2004). Considering the complexities involved the etiology of a particular heart disease the instant specification fails to provide an enabling disclosure, which establishes a mutant form of phospholamban gene, is capable of treating all cardiac diseases. For example considering the instant specification is it is unclear how one skill in the art would treat hypertension or coronary artery disease by administering a mutant phospholamban gene, any fragment thereof or any other gene (as claimed) to the cardiac muscles. The RAC advisory panel clearly emphasized the need for a greater understanding of an underlying mechanism that contributes to a disease along with the pathogenesis of the disease. In addition, besides the use of a phospholamban transdominant negative mutant S16EPLB the specification fails to disclose any other phospholamban mutant, which is capable of enhancing SERCA-2 activity leading enhanced cardiac contractility. In instant case treating a heart disease via a gene based therapy is not considered routine in the art and without sufficient guidance to a specific heart disease or disorder in context of phosholamban gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. see in re wands 858 f.2d 731, 8 uspq2nd 1400 (fed. cir, 1988). it is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. see ex parte Singh, 17 uspq2d 1714 (bpai 1991). Therefore considering the state of the art and limited amount of

guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
PRIMARY EXAMINER
ART UNIT 1633